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PhD dissertation

by

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ENGLISH SUMMARY

Chronic obstructive pulmonary disease is a major public health issue that influences mortality, quality of life and the expenditure of health resources. As yet, we can only imperfectly predict the individual clinical course. This thesis, consisting of three observational, register-based cohort studies explores integrative risk factors in acute exacerbations of COPD and traces changes in the clinical management of exacerbations in Denmark over time.

Study I, which explored previous exacerbations as a risk factor, included 6,656 patients treated with assisted ventilation for exacerbation of COPD. Of these 44% died in-hospital. Patients with previous exacerbations had higher mortality both in-hospital and after discharge. The larger the number of previous admissions, the higher mortality.

Study II, in which changes in the use of assisted ventilation in COPD and mortality were traced, included 173,456 patients. Compared to 2004, a much higher number of patients were treated with assisted ventilation in 2011, and non-invasive ventilation gradually became the dominant mode, while the absolute number of invasive ventilations was stable. In spite of the increase in the number of treatments, mortality was relatively unchanged.

Study III, which explored the association between mortality after an exacerbation and haemoglobin at admission, included 6,969 patients. Mortality with anaemia in-hospital was about twice as high as mortality among patients with normal haemoglobin. After discharge, mortality increased the more haemoglobin deviated from normal values.

In conclusion, this dissertation shows that both previous exacerbations and haemoglobin at admission are risk factors for mortality among COPD patients, and that the introduction of non-invasive ventilation has evoked a profound change in the treatment of severe exacerbations where more patients are treated with assisted ventilation.

DANSK RESUME

Kronisk obstruktiv lungesygdom (KOL) er et betydeligt folkesundhedsmæssigt problem med følger for både dødelighed, livskvalitet of sundhedsudgifter. På nuværende tidspunkt kan vi kun ufuldstændigt forudsige forløbet for den enkelte KOL-patient. Denne afhandling, som består af tre observationelle, registerbaserede kohortestudier undersøger integrative risikofaktorer in forbindelse med akutte forværringer og undersøger ændringer i den kliniske håndtering af disse forværringer i Danmark over tid.

Det første studie, som undersøgte tidligere indlæggelser som risikofaktor, inkluderede 6.656 patienter behandlet for alvorlig KOL-forværring med assisteret ventilation. Af disse døde 44% under indlæggelsen. Patienter med tidligere forværringer havde højere dødelighed både under indlæggelse og efter udskrivelse. Jo flere tidligere AECOPD indlæggelser en patient havde haft, jo større dødelighed.

Det andet studie, som undersøgte ændringer i brugen af assisteret ventilation under KOL-forværringer og den samtidige mortalitet, inkluderede 173,456 patienter. I forhold til 2004 fik langt flere patienter behandling med vejrtrækningsstøtte i 2011 og non-invasiv ventilation blev efterhånden den dominerende ventilationsform mens det årlige absolutte antal behandlinger med invasiv ventilation var stabilt. Til trods for stigningen i antallet af behandlinger ændredes dødeligheden i forbindelse med ventilation sig stort set ikke.

Det tredje studie, som undersøgte sammenhængen mellem dødelighed i forbindelse med KOL-forværringer og hæmoglobinværdien ved indlæggelse, inkluderede 6,969 patienter. Dødeligheden blandt patienter der præsenterede sig med anæmi var dobbelt så høj under indlæggelsen. Efter udskrivelse steg dødeligheden jo længere hæmoglobinværdien var fra normalområdet.

Samlet viser denne afhandling, at både tidligere indlæggelser og hæmoglobinværdier er risikofaktorer for død blandt KOL patienter, og at måden man behandler akutte forværringer af KOL har ændret sig grundlæggende, således at man i dag behandler langt flere patienter med vejrtrækningsstøtte.

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LIST OF ABBREVIATIONS

ACD: Anaemia of chronic diseases

AECOPD: Acute exacerbation of COPD

ARF: Acute respiratory failure

ATC: Anatomical, therapeutical, chemical classification

CCI: Charlson Comorbidity Index

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CPAP: Continuous Positive Airway Pressure

CPR number: Centralt Person Register nummer (the unique personal identifier)

CRS: Civil registration system

DNPR: Danish National Patient Register

eGFR: estimated glomerular filtration rate

GOLD: Global Initiative for Chronic Obstructive Lung Disease

Hgb: Concentration of haemoglobin

HR: Hazard ratio

Htc: Haematocrit

ICD-10: International classification of diseases, 10^{th} revision

ICU: Intensive Care Unit

IDA: Iron deficiency anaemia

IMV: Invasive mechanical ventilation

LFI: Lung function impairment

NIV: Non-invasive mechanical ventilation

NRMPS: National Register of Medicinal Product Statistics

OR: Odds ratio

$PaCO_2$: Partial pressure of carbon dioxide in arterial blood

PaO_2: Partial pressure of oxygen in arterial blood

RCT: Randomised controlled trial

RR: Rate ratio

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INTRODUCTION

The present thesis focuses on exacerbation of Chronic Obstructive Lung Disease, their treatment and risk factors for mortality.

1.1. CHRONIC OBSTRUCTIVE LUNG DISEASE (COPD)

According to the present recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is

> *"a common preventable and treatable disease, … characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases…."* [1]

It is also an extremely diverse and complex disease, the progression of which no intervention has proven efficient in halting[1]. Emphysema, bronchitis and bronchiolitis, the pulmonary hallmarks of COPD, have been recognised for centuries, but the different manifestations were not conceptually unified till the second part of the Twentieth Century [2], and the systemic nature of the disease just begins to unravel. Of large importance in COPD are acute exacerbations, AECOPDs, which are

> "*acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation and leads to change of medication"* [1]

The term exacerbation covers a wide range of clinical presentations, from an aggravation of symptoms manageable in the primary sector to life-threatening acute respiratory insufficiency. Severity of exacerbations can be graded according to the Antonisen criteria [3].

With decreasing severity:

Type 1: Increased dyspnoea AND increased sputum volume AND increased sputum purulence

Type 2: Two of the Type 1 criteria

Type 3: One of the Type 1 criteria AND at least one of the following: upper respiratory infection within the last 5 days, fever without other cause, increased wheezing, increased cough, an increase in respiratory rate or heart rate by at least 20%.

1.1.1. FORMAL DEFINITION OF COPD

Clinically, the severity of the airflow limitation can be assessed with spirometry in stable phase. For the GOLD diagnosis of COPD to be made, the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) must fail to reach 0.7 after administration of a bronchodilating agent. Mild, moderate, severe, and very severe COPD are characterized by FEV1 of more than 80%, less than 80%, less than 50%, and less than 30%, predicted for age, height, sex and race [1]. The GOLD definition has been critisised for underdiagnosing COPD in certain subgroups [4,5].

1.1.2. BRIEF OVERVIEW OF THE PATHOLOGY AND PHYSIOLOGY IN COPD

The pathological development of COPD involves inappropriate inflammation, usually, but not always, provoked by inhaled irritants (tobacco or air pollution)[6–8]. COPD is a disease with conspicuous pulmonary symptoms, but the disease also has a systemic impact with discernible pathological changes in multiple tissues and organ systems.

The relative importance of different pathological processes in the lungs shows inter-individual variation, but emphysema (destruction of the parenchymal tissue), bronchitis/bronchiolitis (inflammation and hypersecretion in the airways) are central processes [9].

Patophysiologically, the consequence of emphysema and bronchitis are [10–12]:

- Expiratory flow limitation
  The resistance to exhalation increases due to diminished elastic recoil, which leads to dynamic airway collapse, and to inflammation, swelling, and mucus secretion in the airways.
- Static hyperinflation of the lungs, by which patients with COPD can to some extent adapt to and compensate for the increased airflow resistance
- Increased mismatch of ventilation and perfusion, which leads to increasing dead-space ventilation and impaired diffusion of oxygen.
- Increased work of breathing, which arises from the increased ventilation, the hyperinflation and the increased airway resistance.

The pathological changes in the lungs are compensated by biochemical compensation. The renal excretion of CO_2 increases as does the concentration of CO_2 in exhaled air,

but the CO_2 level in the blood is reset at a higher level. In stable phases of COPD, this accumulation of CO_2 is counterbalanced and the pH remains normal [13].

Inflammation in the lungs is a cornerstone in the progression of COPD [14] but evidence of inflammatory processes is also present in extrapulmonary tissues. The overarching concept of "systemic inflammation", which is the preferred term in the literature, has been adopted although it has neither been rigorously defined nor conceptually disentangled from comorbidities [15]. Evidence suggests that the balance between pro- and anti-inflammatory processes is shifted towards a state of sustained inflammation in COPD. The effects of this shift are profound and can be measured as altered regulation of inflammatory mediators and functionally in changes in metabolism [16,17]. Multiple biomarkers have been employed as indicators of systemic inflammation in COPD, among others white blood cell count/neutrophils, CRP, IL-6, IL-8, fibrinogen, procalcitonin, erythropoietin and TNF-α, but associations are not straight-forward as inflammatory markers are neither present in stable concentrations over time [18] nor specific for COPD. In spite of this, inflammatory markers do predict future exacerbations [19], accelerated lung function decline [20], and mortality[21].

Profound damage can be observed in organs other than the lungs and and a wide spectrum of diseases are seen among COPD patients more frequently than among age-matched controls [22] . This is hardly surprising as the main risk factor for COPD, tobacco, influences virtually every organ system and other life style risk factors cluster with smoking [23]. Furthermore, the association between COPD and certain comorbidities seems to be stronger than shared risk factors can explain, pointing to a biological interplay [24]. Mechanically, the heart is affected (the cardiopulmonary coupling) [25], and inflammation spills over to or is initiated in other organ systems [17,24,26].

During acute exacerbations, the lungs and airways exhibit further pathological changes often brought about by viral or bacterial infections [27]. There is a clinical overlap between non-pneumonic exacerbations of COPD and pneumonia, but the clinical courses of exacerbations with pneumonia or indeed just with a consolidation on chest x-ray are more severe [28,29].

The major changes in the lungs during a COPD exacerbation are increased airway wall inflammation with oedema, bronchoconstriction, and hypersecretion. In combination, these changes lead to aggravated expiratory flow limitation and dynamic hyperinflation [27]. This again leads to a increased work of breathing. To sustain the alveolar ventilation necessary for adequate gas exchange, the respiratory rate increases and the muscles normally involved in respiration are aided by the auxillary respiratory muscles.

In about 21 % of hospitalised COPD exacerbations these compensatory mechanisms are inadequate [30] and alveolar ventilation cannot be sustained. The hypoventilation results in respiratory (hypercapnic) acidosis often associated with hypoxia and/or metabolic acid-base disturbances, directly caused by hypoxemia or by concomitant comorbidities [13]. Even though the inherent compensatory mechanisms can to some extent prevent a deleterious acidosis [13] , a vicious circle is initiated, which will develop fatally if the work of breathing is not reduced [31].

1.1.3. EPIDEMIOLOGY

COPD is a major causes of mortality and morbidity worldwide, where COPD is projected to be the fourth leading cause of death by 2030 [32]. It has a severe impact on patient quality of life [33] and utilisation of health care resources [34,35]. In Denmark, surveys suggest that about 420,000 citizens fulfill the criteria for COPD [36] and that COPD is stated as the direct cause of about 3,500 deaths per year [37].

COPD is generally known to be underdiagnosed [38] and underreported as the cause of death [39]. Even in the Nordic countries, with comprehensive primary health care systems, the prevalence of undiagnosed COPD is high [40] and formal diagnoses, i.e. those that are spirometrically verified, have only been made in a minority of the patients medicated for COPD [41].

AECOPDs can intercept the progression of COPD at any stage, though they are more frequent in advanced COPD [42–44]. The risk of death is increased during the exacerbation [45,46] and the impact on the further clinical course of survivors is negative with enhanced disease progression [46], diminished quality of life [46,47], enhanced risk of recurrent exacerbations, and increased long-term mortality [43,46].

COPD patients in GOLD stages 2, 3, and 4 experience on average 0.85, 1.34 and 2.00 AECOPDs respectively per year, but only 0.11, 0.25, and 0.54 exacerbations anually lead to hospitalisation [42]. AECOPDs are a common cause of death among COPD patients and in particular among patients with advanced COPD [48]. The overall short-term mortality of exacerbations ranges from 2.1% to 20.4% [35,45,49,50] but patients with severe acute COPD admitted to intensive care are particularly at risk with a six-month-mortality ranging from 25%-40% [49,51,52]. Populations are not directly comparable as the level of care needs that dictates a referral to an ICU may depend on the organisation and level of competence in the medical wards.

Although exacerbations are in general more frequent in severe COPD, recent evidence points to the fact that the occurrence of exacerbations varies extensively among COPD patients with similar lung function in stable periods and that exacerbations are the best predictor of their own recurrence [42,53]. It has been suggested that an inherent “frequent-

exacerbation phenotype" with a distinct pathophysiology [42,54] might explain at least part of the extensive variability in clinical courses.

1.1.4. TREATMENT OF EXACERBATIONS

1.1.4.1 Medical treatment

The first line of treatment of AECOPD is intensified medical treatment with inhaled bronchodilators, systemic glucocorticoids, and antibiotics and, in hospital, supplemental oxygen [1]. This treatment, however, might be insufficient or started too late. In this case, the compensatory mechanisms become overtaxed and fail to ensure sufficient ventilation, the failure of which leads to respiratory acidosis [55,56]. If patients deteriorate even though optimal medical therapy and supplementary oxygen are administered, assisted ventilation is the second line of treatment [1].

1.1.4.2 Assisted ventilation

Mechanism

The vicious circle of insufficient gas exchange can be broken by assisted ventilation. This treatment buys time for the medical treatment to take effect and works by counteracting the deleteriously increased work load imposed by diminished elastic recoil and increased airway resistance.

Assisted ventilation in AECOPD can be administered either invasively or non-invasively. Invasive ventilation (IMV) is administered via an endotracheal tube in the most severe cases of AECOPD, and always under continuous surveillance in an intensive care unit (ICU).

NIV is the technical term for a range of non-invasive treatment modalities. Including, among others, CPAP and BiPAP. NIV always supports the patient's own ventilation, which means that deep sedation is not necessary and that the patient can communicate and have breaks. The support can be given by the application of continuous positive airway pressure (CPAP) or variable pressures timed with the patient's own pattern of ventilation (BiPAP) [57]. It should be noted that the NIV notation is ambiguous and that CPAP is not always included in the "non-invasive ventilation term" [57]. In the present guidelines, CPAP is not recommended for AECOPD in Denmark [58] and will therefore not be further considered here. Throughout this thesis, NIV is used synonymously with BiPAP.

Whereas solid evidence, derived from trials and to some extent from observational studies, supports the superiority of NIV compared to standard medical care in AECOPD [59], few studies have compared NIV to IMV. The sole randomised controlled trial found that the two treatments were associated with equal short-term mortality rates but a trend towards increased 1-year survival in the NIV group [60]. In observational studies, NIV has been advantageous compared to IMV [61–63], but as the studies are observational, causality cannot be directly inferred.

NIV

NIV has been implemented as therapy of choice for hypercapnic respiratory failure in AECOPD. At present, Danish guidelines recommend initiation of NIV in COPD exacerbations if pH≤7.35 and partial arterial pressure of CO_2 ($PaCO_2$) ≥ 6.0 in the absence of respiratory arrest and misfitting masks (absolute) and impaired conciousness, copious secretiong, cardiovascular impairment, danger of vomiting, and claustrophobia. NIV is recommended even in spite of relative contraindications, if advancement orders proscribe intubation [64]. However, NIV seems to be used extensively in both patients with relative contraindications to NIV and in patients without a formal indication for NIV [65]. Studies continuously explore new indications to NIV and challenge the present contraindications [66,67]. Other surveys have, however, found high failure rates upon "off-indication" NIV treatment [68].

A successful outcome of NIV treatment is known to correlate with lower age and rapid reduction of acidosis upon NIV-initiation [69]. NIV failure is likewise associated with older age, low Glasgow Coma Score, severe acidosis and tachypnoea, mixed acid-base disorders, slow or lacking normalisation of pH in addition to poor NIV tolerance and poor adherence to therapy [30,70–73]. Notably, the relation between late failure, i.e. later than 48 hours post NIV-initiation, and immediate improvements in gas exchange seems to be weak [71]. Few studies have examined the association between the previous clinical history of the patient and the outcome of NIV, although the additional risk attributable to being old and male is known [74].

IMV

IMV remains a necessary back-up modality in case NIV is not available, in case of primary contraindications of NIV, and in case of insufficient effect of an initial NIV trial (NIV failure). An initial trial of NIV is often warranted prior to initiation of IMV, but patients with manifest, impending or threatening respiratory or cardiac arrest, i.e. patients with loss of conciousness, haemodynamic instability and apnoea, the airways should be immediately secured by insertion of a endotracheal tube [1].

Prognostic factors following ICU admission for COPD are numerous but few studies have focused solely on patients treated with invasive ventilation and most studies also

include patients admitted to ICU for COPD without ventilation. The in-hospital mortality for COPD patients admitted to ICU is associated with age, sex, comorbidities, cardiopulmonary resuscitation (CPR), resuscitation prior to ICU admission, $PaCO_2$ and acidosis, organ failure and acute severity scoring systems [75–77]. Mortality in the first 6 months after ICU admission is associated with low Glasgow Coma Scale scores, CPR arrest prior to ICU admission, cardiac dysrhythmia, length of hospital stay, and higher values of acute physiology scoring systems [52,78]. Among patients treated with IMV, low haemoglobin has been shown to predict 3 months mortality [79]. Age and hospital length of stay have been shown to associate with 1-year mortality after ICU admission [51]. Comorbidity has been inconsistently associated with mortality [80,81] but conclusions should be drawn with caution as (collider) bias might have been introduced by the selection of patients for ICU and IMV.

In a large European audit, only 51 % and 15 % of patients meeting the criteria for NIV and IMV respectively, had these treatments [82]. This underuse might be partly due to limits of care agreed upon by clinicians and patients at a previous consultation [83], but even among patients without such limitations, assisted ventilation appears to not always be instigated [84]. Possible explanations for this discrepancy are multiple, and probably, though literature in this field is scarce, include overt futility and refusals given by patients on the spot.

Among arguments against or barriers to initiation of assisted ventilation are:

- The chronic and progressive nature of the disease.

Pessimism on behalf of COPD patients is widespread among clinicians and high mortality rates both during treatment and after discharge are expected [85]. In-hospital mortality rates among patients treated with assisted ventilation for AECOPD are in the range of 5 % - 25 % [30,61,62,86,87]. Though an inference of mortality as it would have been if all AECOPD patients with uncompensated ARF were treated with assisted ventilation *per se* cannot be drawn, arguably it would have been higher. Surveys have, however, demonstrated that the prevalent clinical pessimism is somewhat exaggerated especially concerning COPD patients with advanced disease [88]. In addition, even among inevitably dying patients, assisted ventilation, in that case NIV, might be justified for palliative purposes [89]

- Fear of adverse events

Reports on the frequency of complications of ventilation in COPD patients are scarce. The major complications of ventilation are pneumonia, barotrauma, and haemodynamic alterations. Non-invasive ventilation results in fewer complications [90], but 8 - 30 % of NIV patients experience failure in trials [91] and in observational surveys,

5 - 24 % of patients initially treated with non-invasive ventilation have their treatment escalated to invasive ventilation [86,92,93].

- Shortage of capacity

Treatment with invasive ventilation is in general only feasible in ICUs, whereas non-invasive ventilation can be administered in respiratory or otherwise specialised medical wards, however it requires a high nurse-to-patient ratio. That capacity has an impact on the decision to admit a patient to ICUs has been documented but the impact on mortality of restrictions due to bed shortage is not clear [94–98].

1.1.4.3 Choice of mode of assisted ventilation in AECOPD

NIV has only recently been added to the armamentarium for the treatment of AECOPD. The first reports of benefit in AECOPD date back to the early 1980s and the seminal randomised controlled trials were conducted at the beginning of the 1990s [99]. Some countries, e.g. France and the USA, were swift to phase in this new treatment option, whereas it was not endorsed in Denmark until 2003.

Many factors unrelated to the clinical condition of the patient are likely to influence the initial choice of mode of assisted ventilation in AECOPD. Among those, accessibility and capacity [100], case volume, tradition and habits [87,100,101], and the presence of specialised pulmonologists [102] have been documented.

In addition, experience with the choice of ventilator mode continually broadens. Trials of NIV in populations where NIV was previously considered contraindicated have demonstrated that NIV is feasible in, for instance, patients with cerebral depression due to hypercapnia [67]. On the other hand, other studies have demonstrated that NIV failure rates are high among patients with COPD patients with pneumonia [103], low Glasgow Coma Score, high respiratory rate and low pH [104] and have suggested that mortality is higher among patients initially treated with NIV and afterwards transitioned to IMV than among patients initially treated with IMV [86].

Changes in the use of assisted ventilation in AECOPD over time was the focus of study II.

1.1.5. PROGNOSIS

The disease entity COPD covers a diverse range of clinical presentations, the prognosis of which differs markedly. Previously, bronchitis and emphysema were considered distinct disease entities[105]. Patients with dominant emphysema, clinically

presenting with unrelenting dyspnoea, loss of weight, and muscle wasting, were referred to as “pink puffers”. Patients with dominant chronic bronchitis, clinically often presenting with pulmonary hypertension and heart failure, were dubbed “blue bloaters”[106]. These stereotypes are, however, obsolete as they are imprecise and add little to either diagnosis or treatment [9].

COPD patients are, nonetheless, grouped clinically, and different classification schemes have been designed with the aim of predicting morbidity as well as mortality and to qualify choices of treatment for individual patients. The present GOLD recommendations are that COPD patients are classified according to an A to D classification based on lung function impairment, symptoms, and previous exacerbations [1], but this classification has not been shown to supercede lung function per se in prediction of mortality [107]. Other multidimensional indices (the BODE index - BMI, Obstruction, Dyspnoea, Exercise - or the BODE index in combination with the COTE index - comorbidities) have shown predictive values superior to the GOLD classification [108]. That indices which integrate information on functional and metabolic parameters seem to improve prognostication supports the notion of COPD as “more than a disease of the lungs”.

1.1.5.1 Methodological concerns pertaining to the study of prognosis in COPD

Prior to a discussion of prognostic factors, the differences between prognostication in stable COPD patients and prognostication in COPD patients with ongoing exacerbation should be appreciated. These differences might to some extent explain why risk factors in stable phase and acute exacerbations only partly overlap.

Study design: Studies of the prognosis of COPD patients with exacerbation are *per se* inception cohort studies. The inception is, broadly speaking, fixed to a certain point in time (day of hospitalisation, day of discharge etc.) which is determined primarily by the clinical course. In stable phase COPD the study cohort might not even be an inception cohort (patients might all be patients at a clinic or all citizens in a community with a recorded diagnosis of COPD at a given point in time) or the time of inception might to some extent reflect the perceived diagnosis (referral to a specialist clinic or the referral for domiciliary oxygen).

Study population: Exacerbations in themselves are markers of severe disease and/or rapid disease progression[109], and the inclusion of only patients with exacerbations therefore selects a high-risk sub-population in which relations between prognostic factors and outcome might differ from the relations in low risk populations.

Misclassification: A considerable number of COPD patients have not been diagnosed with COPD prior to the first exacerbation [110–113] and therefore cannot have any

reasonably recent measurement of lung function. Comorbidities are underdiagnosed in COPD in general[114] but arguably the rate of underdiagnosis may be different in these diagnosis-naïve patients. Prognostication during exacerbations will therefore to some extent have to rely on factors attainable in the acute phase.

Finally, some prognostic factors might only exist or be revealed during an exacerbation. Infections, while they do play an important role in stable phase COPD, are life-threatening during exacerbations. Also, during an exacerbation the compensatory reserve is explored, as exacerbations constitute periods with staggered physiological equilibria.

The following, not exhaustive, outline of risk factors will focus on mortality during or after exacerbations.

1.1.5.2 The prognostic role of acute physiological derangement

Hypoxia at admission to hospital is strongly associated with both short and long-term mortality [49]. A wide range of other parameters, acidosis, hypercarbia, confusion, respiratory rate, and tachycardia, reflecting the severity of respiratory failure have likewise in different studies been associated with short-term mortality, but data are scarce on the association with long-term outcome.

1.1.5.3 Stable phase severity of COPD and prognosis in exacerbations

Lung function impairment (LFI), gauged in stable phase either as the measured FEV1 relative to FEV1 as predicted from age, height, and ethnicity or as FEV1/FVC, is one of the most extensively studied prognostic factors during exacerbations as well as in stable phase COPD [115]. Since the studies presented in this thesis are register-based no assessments of stable-phase LFI were accessible which is a limitation to the studies. Other relevant severity markers that would have limited confounding in the studies are subjective dyspnoea and use of domiciliary oxygen which both predict both long and short-term mortality[49,116,117].

1.1.5.4 Exacerbations

It is well known that frequent exacerbations are associated with mortality in COPD [118]. The risk of death is high during an exacerbation and mortality remains elevated after lung function and burden of symptoms are restored to pre-exacerbation level [46]. Causal inference should, however, be only cautiously drawn pertaining to exacerbations and long-term mortality. It might be that exacerbations, instead of being causal agents, are instead just markers of severe and rapidly progressing disease.

The association between previous exacerbations and mortality in patients ventilated for AECOPD was the focus of study I.

1.1.5.5 Anaemia

That pulmonary disease evokes changes in the blood and the circulatory system has been long established. As early as 1913, F. Parkes Weber in "The Prognostic Significance of Secondary Polycythæmia in Cardio-pulmonary Cases" [119] presented patients with pulmonary failure and polycythaemia. The presence of polycythaemia was ascribed the to enhanced erythropoiesis in response to tissue hypoxia. Weber recognised the prognostic significance of polycythaemia:

"With the "cardio-pulmonary cases,[…] the outlook is exceedingly grave at the stage of the disease when cyanosis and a great degree of polycytheemia become striking clinical features",

though he did not comment on the significance of anaemia. Interestingly, Weber stated that

"…so far as I can judge, the best marked polycythaemic reactions occur in individuals (especially chronic asthmatics) of Jewish race, and at about middle age, when the reactive powers are stronger than in old age…",

which suggests that, in spite of the somewhat archaic reference to "reactive powers", he appreciated the complexity of alterations to erythrocyte homeostasis in COPD.

Formerly, polycythaemia, and not anaemia, was considered the most important erythrocyte-related disturbance in COPD. From a pathophysiological perspective, polycythaemia is the natural homeostatic response to tissue hypoxia and especially before the introduction of domiciliary oxygen treatment, COPD was an important cause of secondary polycythaemia[120]. Nonetheless, compared to polycythaemia, anaemia has been shown to be far more frequent in modern day COPD populations. Dependent on the population, different types of anaemia predominate, but iron-deficiency anaemia (IDA) and "anaemia of chronic disease" (ACD), and combinations thereof, are most frequently encountered [121].

Iron deficiency anaemia results from depleted iron stores due to either insufficient intake of haemoglobin or excessive loss. The relative importance of these mechanisms is highly dependent on the characteristics of the population but blood loss is a major factor in high-income countries [122]. IDA is prevalent among COPD patients [123] and is associated with negative outcomes [121].

Concentrations of haemoglobin are in general lower in patients with systemic disease (diabetes, heart failure, kidney failure, cancer, chronic infection etc.)[124] which has led to anaemia being considered an inflammatory marker. The mechanisms underlying ACD are complex alterations in iron handling and erythrocyte processing mediated by inflammatory mediators and result in:

- the reduction in the lifespan of erythrocytes;
- the impaired proliferation of erythroid progenitor cells;
- the increased uptake and retention of iron within cells of the reticuloendothelial system (RES). [124].

Multiple studies have addressed the presence and importance of different types of anaemia in COPD and have undertaken extensive biochemical characterisation [16]. Given, however, that the relative frequencies of different types of anaemia have varied highly across populations [123,125], and that the only large studies of prevalence either were conducted in patients with LTOT [126] or in patients where anaemia was only recorded as a diagnostic code [127], we still felt that a study of the mere presence of anaemia and polycythaemia in a large, non-selected cohort was justified and the association between concentrations of haemoglobin and mortality was the focus of study III.

AIMS OF THE THESIS

The overall aim of the present thesis is to add to the understanding of the natural history of COPD and the implications of changing treatment approaches and to improve prognostication.

1.1. HYPOTHESES

On a general level, the hypotheses of the present study are that:

Knowledge of the previous history of AECOPD hospitalisations and the systemic manifestations in COPD can qualify prognostication.

That clinical approach to treatment of AECOPD has become more aggressive and the patients treated more severely ill.

GENERAL ASPECTS OF DATA MANAGEMENT

The studies in this thesis are all based on Danish registers.

The data sources

Danish registers are unique in that they allow easy, unambiguous linkage at the person level. All Danish citizens have a unique personal identifier, a CPR number, assigned upon registration in the Civil Registration System and these are only very rarely changed.

For the studies in this thesis, access to data was provided by Statistics Denmark. Data were provided in an anonymised version where CPR numbers were encrypted. As unlimited data access is not permitted by the Danish authorities, only some variables were provided. The following recapitulation briefly outlines the content of the registers relevant for this thesis.

1.1.1.1 The Civil registration system (CRS)

The CRS provided information on birth, death and sex. The CRS contains information on all persons who are born of a mother already registered in the CRS; have their birth or baptism registered in a Danish electronic church register; or reside legally in Denmark for 3 months or more. One record is generated per person and it contains their date of birth, sex, information on immigration and emigration, and date of death [128].

1.1.1.2 The Danish National Patient Registry (DNPR)

Information on hospital admissions and diagnoses were retrieved from the DNPR. This primarily administrative register is the backbone of the management of hospital activity in the Danish secondary and tertiary sectors and underlies the reimbursement system. A record is generated for each hospital contact with the CPR number of the patient. Additional administrative information provided by the DNPR includes hospital and department, type of admission, and dates of admission and discharge. A record in the DNPR contains at least one diagnosis.The primary diagnosis, which is mandatory, is the main reason for the hospital contact. Secondary and supplemental diagnoses are also occassionally provided but are not mandatory. The DNPR also provides information on procedures. Diagnoses and procedures are chosen from the

Health Care Classification System [129]. In the period of time relevant to the studies included in this thesis, reporting to the DNPR was mandatory for all public or private hospitals.

1.1.1.3 The National Register of Medicinal Product Statistics (NRMPS)

Information on previous medication was obtained from the National Register of Medicinal Product Statistics. The NRMPS contains information on all prescription drugs redeemed at Danish community pharmacies. It hinges on the CPR number and provides information on dates of redemption, ATC codes, and units of medication dispensed. Only prescriptions that were actually redeemed are recorded, and the register does not contain information at the patient level on over-the-counter medication[130]. Of note, the medications on which information was retrieved in this study cannot be purchased over-the-counter at Danish pharmacies and patients are partially reimbursed upon purchase. Arguably, this makes significant unregistered use improbable.

1.1.1.4 The paraclinical dataset

In contrast to the abovementioned registers, this dataset is not an official register with nationwide coverage. Instead, the dataset contains blood sample results from hospital laboratories and external laboratories, which have chosen to sign up. Laboratories have joined at different points in time and some have only provided results from a limited period of time. Each laboratory result is recorded along with the name of the test, the CPR number of the patient and the date of sampling. To some extent the laboratory where the sample was analysed can be identified. Of note, the laboratories report their own name for any given test and the test results mirror the calibration of the individual laboratories and can therefore be subject to variation.

Definitions used in the studies

"Admissions" were retrieved from entries in the DNPR, but admissions were merged if the date of discharge in one admission equalled the admission date of another.

"AECOPD admissions" were defined as admissions with either a primary diagnosis of COPD (ICD-10: DJ44) or with a combination of either acute respiratory failure (ICD-10: DJ96) or pneumonia (ICD-10: DJ13-18) with COPD as a secondary diagnosis. Admissions of patients less than 30 years of age were excluded from the cohort to minimise inclusion of misclassified asthma.

"Respiratory admissions" were defined as admissions where the primary diagnosis was within the ICD-10 DJ-spectrum.

"Ventilation" had occurred whenever IMV (BGDA0) and/or NIV (BGDA1) was coded during a AECOPD hospitalisation.

"AECOPD Readmissions" were admissions for AECOPD in patients who had previously been admitted for AECOPD.

PRESENTATION OF STUDIES

Three studies (I-III) are included in this thesis.

1.1. STUDY I

1.1.1.1 Aim

To investigate the relationship between the number of previous hospitalisations for AECOPD and prognosis in a population of patients with severe AECOPD.

1.1.1.2 Study subjects

The cohort of participants in study I were patients who had been treated with assisted ventilation for AECOPD for the first time. Patients who had not redeemed medication for obstructive airway diseases in the year preceding hospitalisation were excluded. Figure 1[131] outlines the selection of patients for the cohort.

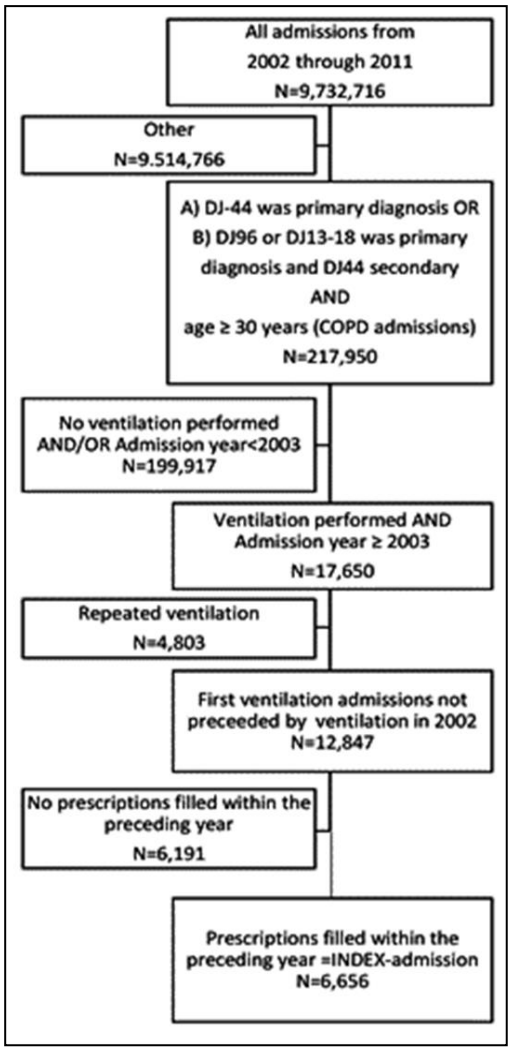

Figure 1 The selection of patients for the study I cohort.

1.1.1.3 Methods

To address the association between previous AECOPD admissions and mortality two models, for mortality in-hospital (1) and mortality after discharge (2) respectively, were fitted.

Model 1: Sex, time periods, Charlson Comorbidity Indices, mode of ventilation and the number of previous hospitalisations as factor variables and age at admission as a

continuous variable were fitted into a logistic regression model with in-hospital mortality as a binary outcome. Age was included in the model as a continuous covariate as the estimates were linear. Interactions between previous hospitalisations, and age, sex, and mode of ventilation were tested for by comparisons of likelihood but none were significant.

Model 2: A Cox proportional hazards model was fitted with survival time after discharge as the dependent variable and the number of previous hospitalisations as independent factor variables along with sex, time periods, and Charlson Comorbidity Indices and mode of ventilation. We visually assessed the proportional hazards assumption by plotting Schoenfeld residuals.

1.1.1.4 Results

There were more than 200,000 admissions for AECOPD from 2003 through 2011 but less than 7,000 were eligible for inclusion in the cohort. As can be seen in Figure 2 [131] the majority of patients had had no AECOPD hospitalisations in the year preceding the ventilation.

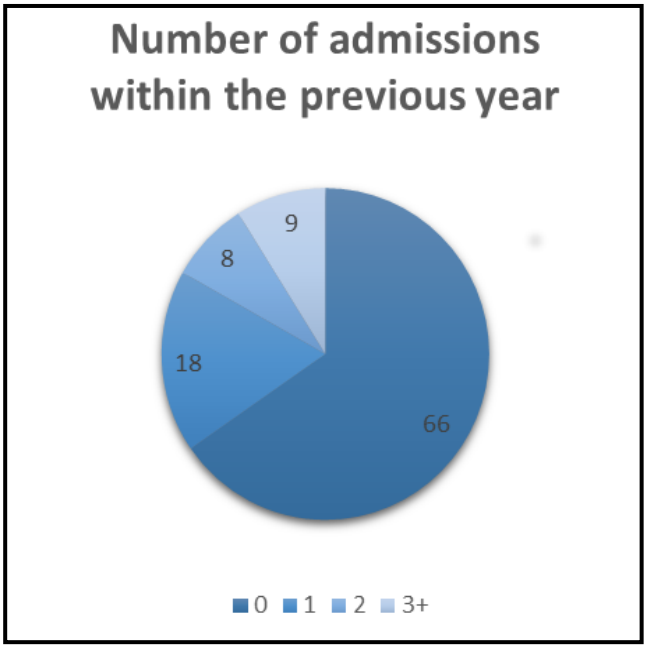

Figure 2 The distribution of the number of admissions in the preceding year for the patients included in study I.

Mortality in-hospital of the entire cohort was 45%. Eleven percent of patients discharged alive died within a month and 39% within a year. Figure 3 [131] shows the mortality after admission for the entire cohort.

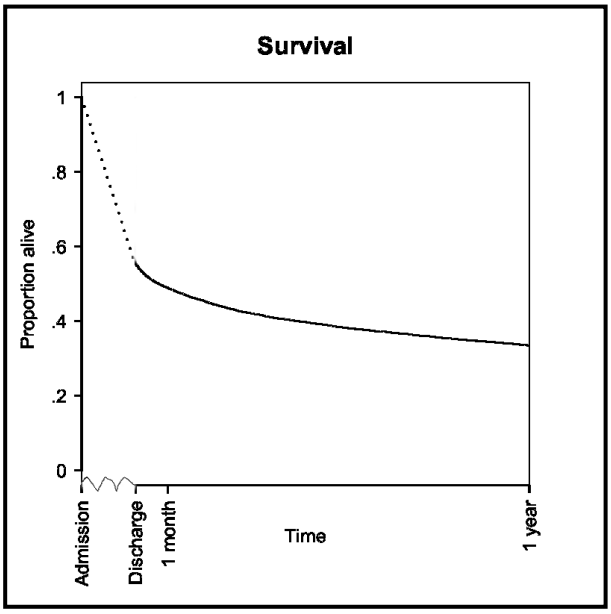

Figure 3 Mortality after admission for all patients included in study I. The beginning of the abscissa has been manipulated to hold hospitalisations of different lengths.

The main finding of the study was an increased risk of death both in-hospital and after discharge with each additional previous hospitalisation for AECOPD. This association was present independently of age, sex, number of comorbidities, mode of ventilation and time period. **Fejl! Henvisningskilde ikke fundet.**Table 1 presents adjusted estimates of the odds and hazard ratios with prior hospitalisations, and an increasing risk with each prior admission can be discerned. The substitution with respiratory admissions for COPD admissions gave a weaker association but in the same direction.

	Number of admissions for AECOPD in the preceding year			
	0	1	2	3
In-hospital death				
Adjusted OR	1 (ref)	1.26 [1.11-1.44]	1.43 [1.19-1.72]	1.56 [1.30-1.87]
Death beyond discharge				
Adjusted HR	1 (ref)	1.32 [1.19-1.46]	1.76 [1.52-2.02]	2.10 [1.80-2.38]

Table 1 The risk of death before and after discharge respectively, by the number of AECOPD hospitalisations in the preceding year.

Interestingly, IMV was associated with higher risk of death in-hospital (OR 1.71 [1.53-1.90]) compared to NIV but lower risk after discharge (HR 0.77 [0.71-0.84]).

A separate analysis was performed, in which all admissions ascribed to respiratory causes were substituted for COPD admissions, but this made little difference to the associations.

1.1.1.5 Main conclusions

Study I demonstrates that the prognosis following ventilation for AECOPD is grim and provides evidence that the previously demonstrated link between frequent exacerbations and mortality does not just reflect a propensity for severe exacerbations among frequent exacerbators.

1.2. STUDY II

1.2.1.1 Aim

To outline the development in the use of assisted ventilation in AECOPD and the associated shifts in mortality.

1.2.1.2 Study subjects

The participants in study II were 173,456 AECOPD patients admitted to hospital in the time period from 2004 through 2011. Subgroups, which either encompassed all patients ventilated during an AECOPD admission or patients ventilated for the first time during an AECOPD admission, were established.

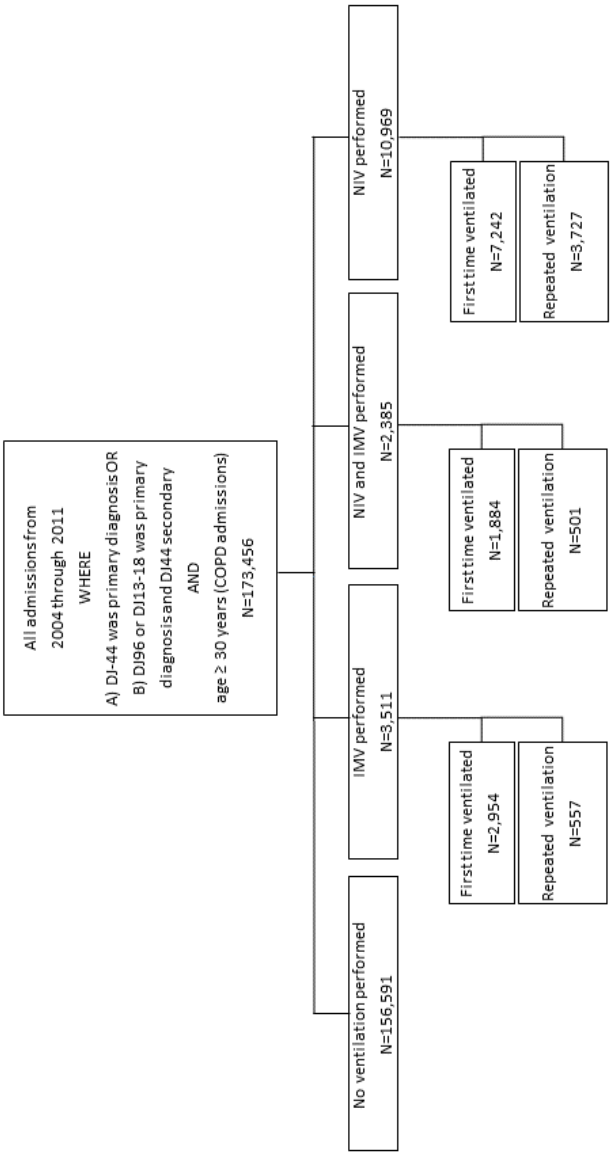

Figure 4 The selection of patients for study II.

1.2.1.3 Methods

We established the annual number of admissions and ventilations. To explore any trends in these numbers, we employed the Kendall τ rank correlation test, which identifies monotonic relationships irrespective of non-linearity. We used ANOVA to test for trends over time in mean age at first ventilation.

Temporal changes in in-hospital mortality and mortality and/or readmission within one year after discharge were explored with Poisson regressions. Annual numbers of admissions were used as the offset and the proportion of patients who died in-hospital or died/were readmitted within a year was the dependent variable. Year was added to the model as a numerical covariate and the coefficient expressed as odds ratio per 5 years increases. The model was adjusted for distribution of age, sex and Charlson Comorbidity indices. We visually assessed potential non-linearity by adding year as a categorical variable, instead of the numercal year, and plotting the year-coefficient association.

1.2.1.4 Results

The use of assisted ventilation for AECOPD increased in the time period as is depicted in Figure 5, panel A. There was very little variation (<10%) in the annual total number of AECOPD admissions, which ranged from 20,959 per year to 22,863 per year. Assisted ventilation was, in contrast, administered to a larger proportion of patients over time.

The relative use of the different modes of ventilation changed over time, as can be seen in Figure 5, panel B. NIV became the dominant mode, and in 2011 more than half of IMV treatments were given to patients who also received NIV during the same hospitalisation. Nonetheless, the use of IMV did not change. The increase in the use of assisted ventilation and the shifting of modes were not solely driven by multiple ventilations of the same patients at later hospitalisations as can be seen in Figure 5, panel C.

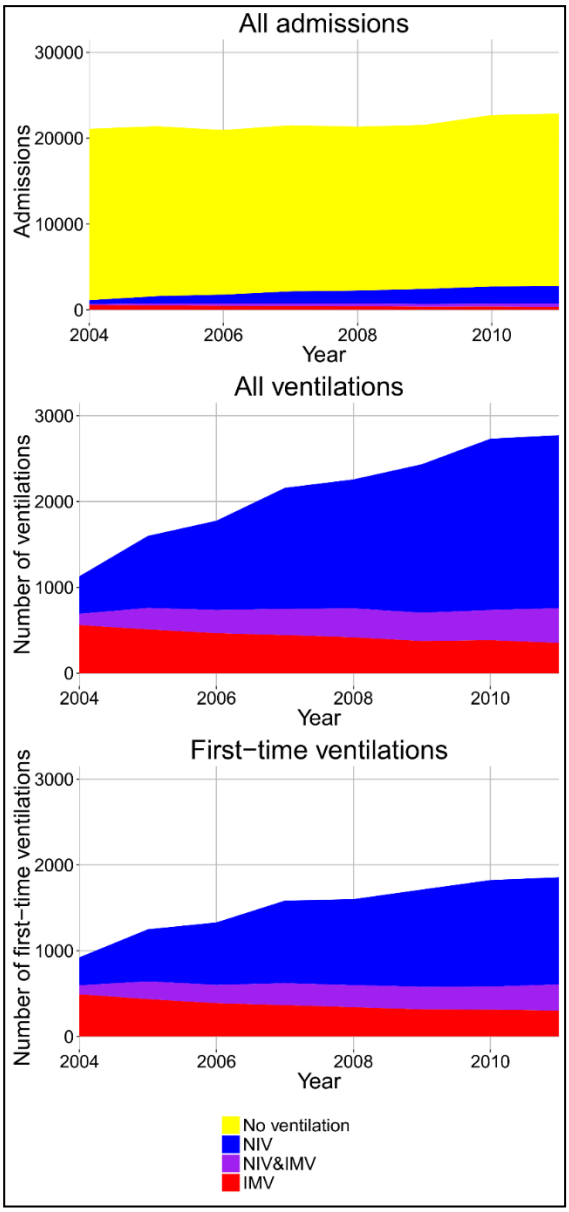

Figure 5 The annual number of AECOPD admissions.

A: All AECOPD admissions.

B: AECOPD admissions were ventilation was performed.

C: AECOPD admissions where the patient had not been ventilated for AECOPD before.

Development in mortality rates by mode of ventilation can be seen in Figure 6. Panel A shows the in-hospital mortality rates among all first-time ventilated patients. The time-averaged mortalities among patients receiving the different modes of ventilation were different (χ^2: $p<0.0001$). Mortality was lower with NIV than mortality among patients treated with both IMV ($p<0.0001$) and NIV and IMV ($p<0.0001$) but there was no difference between mortality among patients receiving IMV alone and patients receiving both IMV and NIV ($p=0.99$). Panel B shows rates of 1-year mortality among first-time ventilated patients discharged alive. The pattern resembled the in-hospital mortality in that there was a significant difference overall ($p<0.0001$) among patients receiving NIV and IMV ($p<0.0001$), and NIV and NIV in combination with IMV ($p<0001$), but no significant difference between patients receiving NIV in combination with IMV, and IMV ($p=0.09$).

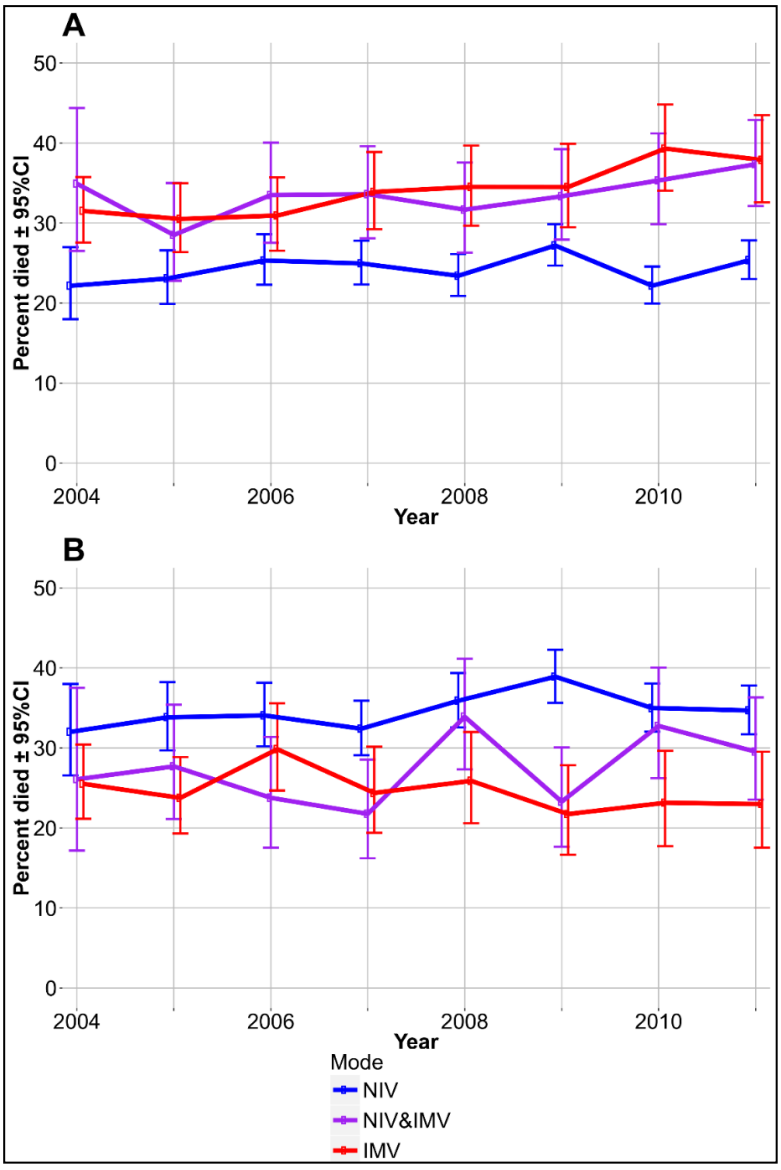

Figure 6 Development in mortality rates by mode of ventilation over time.

Panel A: in-hospital mortality rates among all first-time ventilated patients.

Panel B 1-year morality rates among first-time ventilated patients discharged alive.

The adjusted temporal development in mortality can be seen in Table 2. The adjusted rate ratios of death in-hospital increased for patients treated with IMV overall. Mortality after discharge did not change following either mode.

	NIV	IMV	All IMV
Mortality ratios for death per 5 years			
Unadjusted	1.03 (0.92 - 1.15)	1.18 (1.04 - 1.35)	1.16 (1.04 - 1.29)
Adjusted†	0.95 (0.85 - 1.07)	1.12 (0.98 - 1.28)	1.12 (1.01 - 1.25)
Mortality ratios for death within a year per 5 years§			
Unadjusted	1.06 (0.95 - 1.18)	0.91 (0.75 - 1.11)	1.02 (0.88 - 1.18)
Adjusted†	1.00 (0.90 - 1.11)	0.85 (0.70 - 1.04)	0.99 (0.85 - 1.15)

Table 2 Risk of death before discharge and 1 year after discharge for first time ventilated AECOPD patients.

Adjusted for age, sex and Charlson Comorbidity score.

§: Only patients who survived to discharge

1.2.1.5 Main conclusions

Study II shows that more patients with AECOPD are being ventilated during hospitalisation and that non-invasive ventilation has become the mode most frequently used. The use of invasive ventilation has been stable. This, along with an increased mortality among patients treated with invasive ventilation at least suggests that not only are more patients being offered ventilation but they are also increasingly being offered ventilation in spite of severe illness.

1.3. STUDY III

1.3.1.1 Aim

To investigate the distribution of concentrations of haemoglobin in AECOPD patients and explore the relationship between concentrations of haemoglobin and mortality.

1.3.1.2 Study subjects

The cohort of participants in study III consisted of 6,969 patients who were admitted to hospital for AECOPD for the first time from 2007 through 2012 (**Fejl! Henvisningskilde ikke fundet.**). Only patients admitted to hospitals from which we have access to recorded blood test results were included.

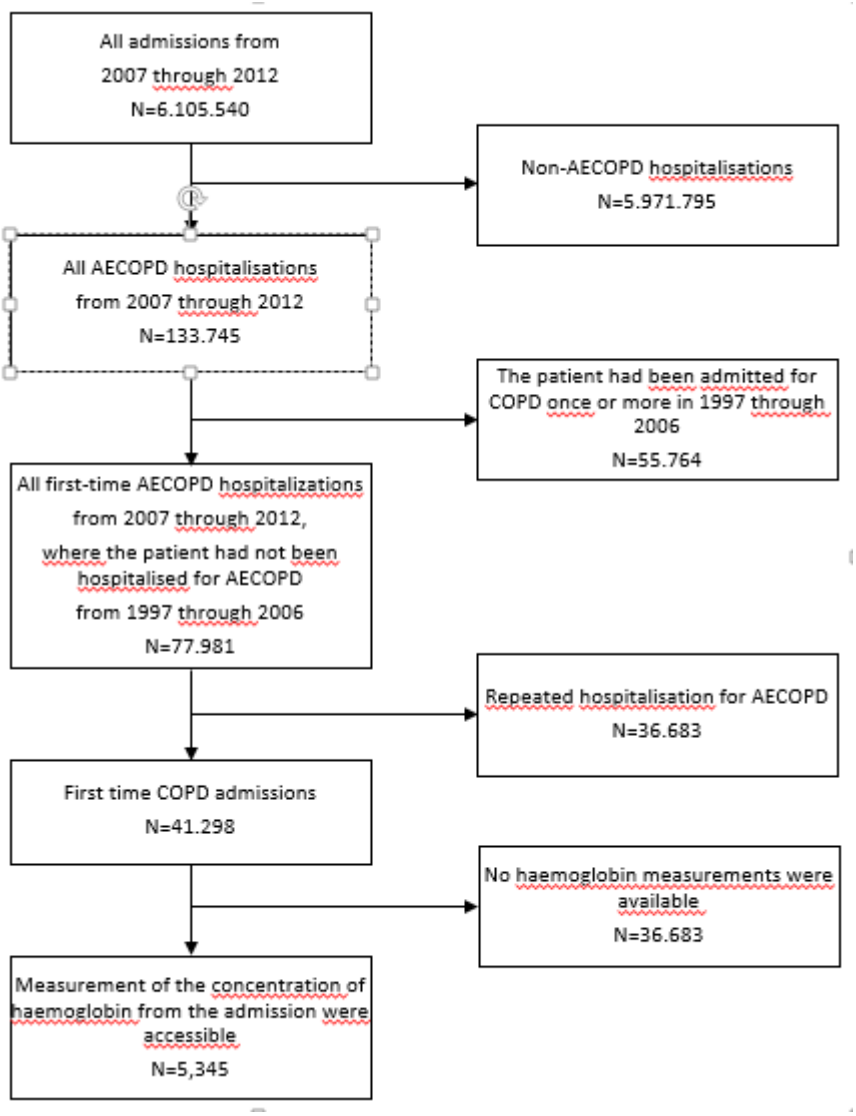

Figure 7 The selection of patients for the study III cohort.

1.3.1.3 Methods

For each member of the cohort, we retrieved information on haemoglobin at admission, renal function, and selected comorbidities, either through recordings in the DNPR or through redeemed prescriptions.

The WHO definition of anaemia [132] was applied along with a definition of polycythaemia proposed by Chambellan et al [126]. Based on the first haemoglobin measurements made during the hospitalisation patients were divided in three groups: anaemia, normal haemoglobin, and polycythaemia.

To capture the relationship between levels of haemoglobin and mortality after discharge we built univariate and multivariate Cox regression models. Different models were built for men and women and models were adjusted for renal function and comorbidity.

Subgroup analyses were made firstly among patients who had redeemed medication for COPD and secondly among patients who had none of the selected comorbidities and renal function in the upper 3 quartiles.

1.3.1.4 Results

In our cohort, 30.9 % of the patients had anaemia at admission, but it was more common among males, 39.1 %, than among females, 23.8 %. Polycythaemia was found in 2.6 % of males and in 13.8 % of females. Baseline characteristics at admission and outcomes are presented in Table 3. Mortality was higher both in-hospital and after discharge among anaemic patients (both $p<0.0001$).

	Anaemia at admission	Normal haemoglobin at admission	Polycythaemia at admission	Total
	n=2,152	n=4,213	n=604	n=6,969
Male	1,257 (58.4%)	1,870 (44.4%)	85 (14.1%)	3,212 (46.1%)
Age/years,median (IQR)	78.0 (70.0 - 83.8)	73.3 (64.0 - 80.2)	70.5 (61.9 - 77.1)	74.7 (65.4 - 81.2)
Medication for obstructive airway diseases	1,468 (68.2%)	3,035 (72.0%)	433 (71.7%)	4,936 (70.8%)
Antidiabetics	287 (13.3%)	402 (9.5%)	38 (6.3%)	727 (10.4%)
Antithrombotics	1,218 (56.6%)	1,718 (40.8%)	202 (33.4%)	3,138 (45.0%)
ACE- and AT2R inhibitors	910 (42.3%)	1,376 (32.7%)	172 (28.5%)	2,458 (35.3%)
First haemoglobin, median (IQR)	114.4 (106.3 - 119.2)	138.6 (132.1 - 146.6)	157.9 (154.7 - 167.6)	133.7 (120.9 - 145.0)
First eGFR	64.0 (42.0 - 87.0)	76.0 (57.0 - 96.0)	76.0 (59.0 - 98.0)	72.0 (53.0 - 94.0)
Died in hospital	249 (11.6%)	217 (5.2%)	42 (7.0%)	508 (7.3%)

Table 3 Baseline variables and hospital outcome in the study III cohort by haemoglobin category.
Anaemia: Males: haemoglobin<130 g/L, Females: haemoglobin < 120 g/L.
Polycythaemia: Males: haemoglobin>170 g/L, Females: haemoglobin>150 g/L

Uni- and multivariate variate analyses of the association between levels of haemoglobin and mortality after discharge are presented in Figure 8. The association between haemoglobin and mortality was inversely but non-linearly associated with haemoglobin below the WHO normal range.

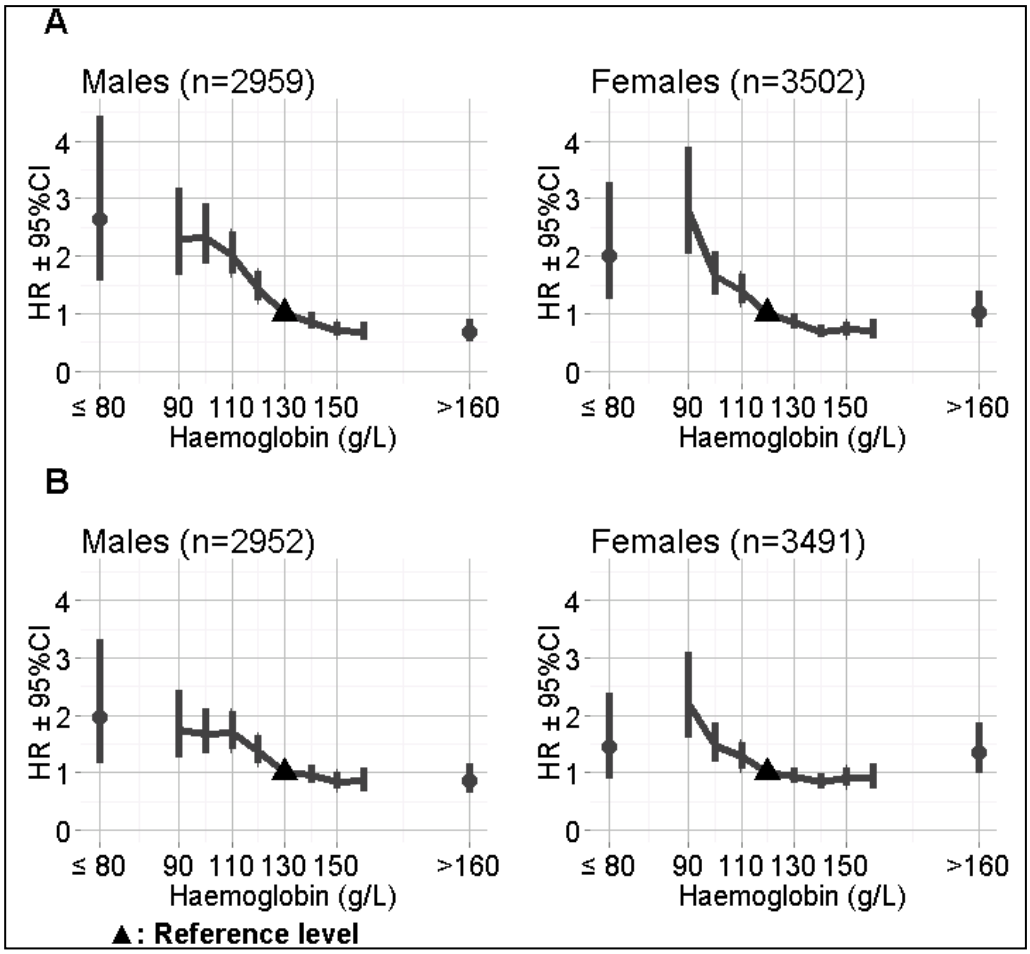

Figure 8 Risk of death after discharge for patients discharged alive by concentration of haemoglobin. Measurements are rounded to nearest 10 g/L.

A: Unadjusted

B: Adjusted for age, use of antidiabetics, use of ACE and/or AT2R-inhibitors, use of antithrombotics, quantile of lowest eGFR, cancer, heart failure and AMI. Only patients with measurements of both haemoglobin and eGFR were included.

1.3.1.5 Main conclusions

Study III demonstrates that anaemia, in contrast to polycythaemia, is frequent among patients admitted to hospital for AECOPD. The study furthermore demonstrates that there is an association between levels of haemoglobin and mortality and that mortality

is significantly higher among patients with only mild anaemia compared to patients with normal haemoglobin.

DISCUSSION OF METHODOLOGY

In this chapter the methods used and their appropriateness in all three studies are discussed.

1.3.1.6 The study population

Due to the unambiguous data linkage in Danish registers it was possible for us to avoid inclusion of patients more than once in the cohorts. This is pivotal from a statistical perspective, as repeated inclusion of the same subjects in models violates the assumption of independence of observations underlying the simpler regression models applied here [133].

Patients who were hospitalised for AECOPD and ventilated for this for the first time were included in the study I cohort, provided they had redeemed medication for obstructive pulmonary disorders at least once within the preceding year. The decision to restrict the study population to only previously medicated patients was taken for two reasons: firstly, as we did not have access to measurements of lung function impairment prior to the exacerbation, we wanted to narrow the range of impairment as much as possible. It has been previously demonstrated that the recognition of COPD in a patient is associated with the degree of lung function impairment [113] and, arguably, the exclusion of patients who had not been medicated shifted the cohort towards patients with severe impairment. The trade-offs are selection which might introduce systematic bias and that generalisability is restricted. Secondly, it might be argued that the inclusion of patients who, in spite of numerous admissions ascribed to COPD exacerbation, had not redeemed any prescriptions, had been misdiagnosed and whose misdiagnosis at subsequent admissions had been passed on.

The analyses in study III were restricted to first-time admitted patients whose haemoglobin measured at admission was accessible in our register. Whereas there is little reason to suspect bias due to the selection of hospitals, it is reassuring to notice that only a very small fraction of patients admitted to relevant hospitals lacked haemoglobin measurements, as bias could have been introduced by severely ill patients dying before blood samples could be drawn.

1.3.1.7 Assessment of exposure and outcome

In study I, the number of hospitalisations for AECOPD in the year preceding the first ventilation for AECOPD was chosen as a proxy for the previous clinical history of the patient. Only a fraction of actual AECOPDs leads to hospitalisation and arguably, the total number of AECOPDs in the previous year, and not just the AECOPDs that led to hospitalisation, would have been a biologically more meaningful variable. It is possible to define an indicator of AECOPDs that have been dealt with in the primary sector through assessment of prescriptions redeemed by the patient [134], but this approach was not chosen here as it has, to our knowledge, not been validated, and as the recommendations for handling of AECOPD are in general poorly complied with [135].

In study III, the first haemoglobin measurements were used to predict mortality. While unambiguous, the first haemoglobin measurement might reflect not only the value at admission but rarefication due to fluid infusion given before the sample was drawn and concentration due to diuretics. As such the first haemoglobin would not capture the true haemoglobin at admission. Though "anaemia", according to the Oxford English Dictionary, literally means "A condition in which there is a deficiency of red cells or of haemoglobin in the blood", this simplistic definition fails to capture the complexity of anaemia as a pathological entity. Anaemia has multiple links to nutrition, metabolism, inflammation, infection, genetic build-up, organ failure and malignancy and the relative importance of these factors differs vastly globally and across age groups [136]. While we used measured intervals of haemoglobin concentrations in survival models, we described the prevalence of anaemia in our population according to the WHO definition. The WHO sets different reference ranges for men and women, but does not address the differences known to exist across age groups and ethnicity [137]. The WHO reference values are easily applied and widely used, but their construct validity has been contested in light of this heterogeneity [138]. We compared our prevalence estimates to estimates found in the literature only after a standardisation to the WHO anaemia definition and the distribution across the sexes in our population, but - aware of disagreement on this point – we should have liked to standardise distributions of age and ethnicity as well. It is possible that divergent estimates reflect these baseline demographics rather than biologically and clinically relevant differences across populations.

1.3.1.8 Temporal changes

Absolute numbers of treatments might be of some interest from a organisational perspective but in order to understand clinical practice, relative numbers are needed. In other words, what is the likelihood of being having a treatment given a set of

baseline characteristics at different points in time? As these baseline characteristics are not routinely recorded, any answer to this relies on the rather strong assumptions of both unchanging incidence and unchanging baseline characteristics, and these assumptions allow employment of absolute numbers as a proxy for likelihood. These assumptions are, however, challenged by previous Danish studies, one of which found that the incidence of hospitalisations decreased in spite of a constant prevalence of COPD that had at some point required hospitalisation in the period from 2002-2009 [139]. Another study found that the use of intensive care, the burden of comorbidity, all-cause previous hospital admissions, and mortality increased, thereby prompting suggestions that the severity of disease among patients hospitalised for COPD was increasing [140].

1.3.1.9 Statistical modelling

The DNPR does not permit reconstruction of the time sequence of treatments initiated during hospitalisation. Therefore, in study I and II it is not possible to establish the date at which ventilation was initiated. When in-hospital mortality is assessed as a binary outcome, the need to establish the exact day of entry into the cohort is circumvented. However, what cannot be dealt with so easily is the immortal time bias that might have been introduced by different time to initiation of ventilation across exposure groups (i.e. groups with different numbers of previous hospitalisations). Immortal time bias is "created when there exists a period of time during which the outcome of interest […] for one of the cohorts cannot possibly occur" [141] and can severely affect the validity of estimates in survival analysis[142]. If, for instance, ventilation happens to be initiated at the admission day among patients in study I who have had many AECOPD hospitalisations (e.g. because COPD is recognised immediately) and not till day 2 in patients who have not been hospitalised for AECOPD before (e.g. because it takes time to recognise the condition), the latter group will have been "statistically immortal" for two days. The association between previous hospitalisations and death would therefore tend to be exaggerated.

1.3.1.10 Misclassification

Misclassification is erroneous assignment of either exposure, covariates, or outcome to study records. It can be either non-differential (i.e. the probability of erroneous assignment is the same for all records) or differential (i.e. the probability of erroneous assignment is higher in subsets of records) and both kinds may lead to bias.

Diagnosis of AECOPD

To isolate hospitalisations for AECOPD in all 3 studies, we followed the definition described by Thomsen et al. [143] where "COPD-hospitalisations" were hospitalisations

of patients of at least 30 years of age with either a primary diagnosis of COPD (ICD-10: DJ44) or with a combination of either acute respiratory failure (ICD-10: DJ96) or pneumonia (ICD-10: DJ13-18) as the primary diagnosis and COPD as a secondary. The positive predictive value for COPD of this definition was 92%, but 19% of patients coded for either pneumonia or respiratory failure but not COPD had underlying COPD. The negative predictive value is unknown.

The definition of COPD exacerbations relies on the clinical presentation of the patient [1] and clinical recognition of underlying COPD in a patient in respiratory distress depends on either a previous diagnosis of COPD or a clinical history suggestive of COPD, as lung function impairment cannot be assessed during exacerbations. COPD is underdiagnosed [38] in the general population as well as in patients admitted to hospital for respiratory complaints [110]. Furthermore, it is only mandatory to enter one diagnosis per patient record to the Danish National Patient Registry.

Most, but not all, exacerbations are precipitated or complicated by infection [144] and there is no sharp demarcation between exacerbations and pneumonia in COPD, though the aetiology and outcomes are different [116]. Also, the extent to which COPD patients hospitalised for reasons other than exacerbation are filed in the register with a primary diagnosis of COPD is unknown but it is known that it can be clinically challenging to distinguish exacerbations from day-to-day decline in end-stage COPD.

In summary, it is possible, that many true exacerbations of COPD are missed while admissions of COPD patients for reasons other than exacerbations/pneumonia are erroneously included, when the abovementioned definition is applied.

The inclusion of patient records where COPD exacerbation was not the real reason for admission and the exclusion of true COPD exacerbations limit the validity of the study.

The probability of a COPD diagnosis being assigned, given COPD in the subject in question, may depend on the severity of lung function impairment and acute derangement. In study I, from a validity perspective, this is problematic as it potentially contributes to differential misclassification. In an effort to circumvent bias introduced by misclassification of prior COPD admissions, a separate analysis was performed, in which all admissions ascribed to respiratory causes were substituted for COPD admissions. There was an association with mortality that resembled the association with COPD admissions, which argues against a large impact of misclassification.

As previously mentioned, we differentiated in study I between first time ventilations, which were preceded by filled prescriptions for drugs used in obstructive airway disease, and first time ventilations, which were not. In fact, among patients who had

not redeemed any prescriptions for COPD medication in the preceding year, an increasing number of previous COPD-admissions was associated with a decreased risk of death in-hospital. In itself, this serves as a reminder of the dangers inferred by an assumption of a direct correspondence between register and reality. A possible explanation for this biologically absurd finding is that a patient by not having any COPD medication prescribed or redeemed after an admission for COPD is selected or selects himself as a patient whose prognosis is particularly good, probably because the diagnosis of COPD is wrong or the disease is in an early stage.

Diagnoses of comorbidities

The Charlson Comorbidity Index (CCI) was originally developed for prognostication of 1-year survival from medical chart review in medical patients [145]. The index encompasses a number of comorbidities and points are assigned for each comorbidity proportionally to the association between that comorbidity and mortality. In some adaptations, points are assigned for advancing age. The index has been extensively modified to be calculated from medical registers and validated in different populations [146]. The application of the Charlson Index in register-based studies has the advantages of producing one integrated parameter from a lot of different diseases, of being easy to calculate and - at a glance – being easy to interpret. There are, nonetheless, noteworthy problems.

Firstly, a register-based calculation of CCI has not been directly validated in a population of patients with exacerbations of COPD. Therefore, the assignment of a given number of points to different diseases, originally meant to reflect the prognostic impact of these diseases might weigh too heavily or too lightly in a population of present day AECOPD patients. To our knowledge, only a Canadian study has made a direct attempt to validate CCI in COPD patients [147]. The study demonstrated that CCIs based solely on hospital admission registers had an acceptable precision for predicting 1-year mortality among incident and prevalent COPD cases, but the frequencies and impacts of different comorbidities might be different in a population admitted to hospital for exacerbations, as this population might differ from COPD patients in stable phase.

The Danish National Patient Registry consists of entries of the diagnoses that were the main reasons for admissions or out-patient visits and in some cases a secondary or supplementary diagnosis [129]. As such, the validity of the registration is highly dependent on the disease in question. The positive predictive values of diagnoses in the DNPR are in general high [148], but little is known about the negative predictive values. In simple cases with non-differential misclassification of a confounder variable, underreporting results in residual confounding and estimates of the effect of the primary variable inbetween the unadjusted and the fully adjusted values, but the implications in study I and study II might be more complex. Firstly, there is probably an association between the number of admissions and the chance that any comorbidity

present has been registered, leading to non-differential misclassification in study 1. Secondly, Charlson Comorbidity Indices are incorporated in our regression models as a categorical (in this case, three-level) variable and as such, might introduce non-differential misclassification [149].

Code-drifting A potential problem in relation to the coding system in Danish registers that is not well described is the consistency of coding practice over time. We know from American studies that clinical recording can change rapidly in response to changes other than shifts in the actual incidence of a disease entity [150]. The DNPR is mainly set up for administrative purposes and measures of activity at individual hospital units are derived from it. Reimbursement might differ severalfold with different but arguably accurate diagnostic codes and a drift towards more "expensive" codes is likely to have taken place. In the American study the code drifting had profound consequences for the estimates of mortality in consecutive years which might lead to erroneous conclusions. Our inclusion of patients is based on diagnostic codes and it is reassuring that the number of admissions to hospital for AECOPD in study II was nearly constant across the study period. We cannot, however, rule out that a drift in case mix between subgroups biases our results.

1.3.1.11 Confounding

"Confounders are factors (exposures, interventions, treatments, etc.) that explain or produce all or part of the difference between the measure of association and the measure of effect that would be obtained with a contrafactual ideal" [149]. A serious limitation, that in fact pertains to all studies, is the lack of assessment of physiological status which might constitute such a confounder. The Danish registers contain only sporadic information on stable phase lung function and acute deterioration. The inclusion in study I of only patients in need of assisted ventilation only partly eliminates this source of unmeasured confounding. Physiological assessments are under certain circumstances reported in patients seen in out-patient clinics, as part of a quality surveillance, and these data were retrieved. Upon examination, it became evident that these data, while they enabled an adjustment for FEV1 in a small subgroup of patients, were prone to confer confounding by indication. Therefore, it was decided not to adjust for FEV1.

Whether to consider a coexisting condition a comorbidity in its own right or a component in COPD has an impact on how to address its presence in survival models. Considering a comorbidity an independent coexisting condition allows direct adjustment. In contrast, a comorbidity that reflects the severity of COPD cannot be directly adjusted for, as this would lead to bias [149]. As an example, COPD patients more frequently have cardiovascular disease compared to patients without COPD [22]. This might just reflect a shared risk factor, smoking, but there is also evidence for an

association that is independent of smoking [151]. By adjusting for CCI, which includes previous AMI, we might unintentionally have partly adjusted for the severity of COPD. The same considerations apply to the association between concentrations of haemoglobin and COPD in study III.

Estimates of prevalence are relevant only if the selection of the population that gave rise to the estimate is clearly described and if this population forms a logical and operational entity. Our population was all first-time admitted AECOPD patients, whose selection is relevant from an organisational-clinical perspective as intervention could potentially be instigated at this point, and from a research point of view as haemoglobin is not – to our knowledge – associated with acceleration of the first hospital admission. Our prevalence should not be interpreted as describing the prevalence in the COPD population as a whole, as there might be huge differences between the prevalence in patients with and without exacerbations and at different points along the COPD trajectory.

DISCUSSION OF RESULTS

1.3.2. STUDY I

The prognostic role of the clinical history has been assessed in many studies [43,46,47,134,152–169]. Previous exacerbations are known to predict mortality in AECOPD, but to our knowledge we are the first to address the association in a population of patients with uniformly severe AECOPD.

From what was known when we commenced our study, it could not be inferred whether the association between hospitalisations and mortality just reflects a propensity among frequent exacerbators for development of severe exacerbations with an inherent high fatality rate. Alternatively, the association is completely or partly independent of AECOPD severity. The association found between the number of previous associations and mortality in our study lends support to the latter.

We can only speculate about the pathological linking of previous exacerbations and mortality. The association might reflect that the underlying lung function impairment is more severe among frequent exacerbators or that the frequent exacerbators have to a larger extent not yet recovered from the latest exacerbation, a process which might take months [170] or might never be completed [171]. Alternatively, the frequent exacerbators in our study might be frequent exacerbators because of pre-ventilation frailty, whose frailty has lowered the threshold for hospital admittance in the year prior to the ventilation. It is also possible that frequent and rare exacerbators experience exacerbations with fundamentally different underlying pathology. Differences in the presence and nature of microbiological agents across frequent and non-frequent exacerbators have been demonstrated [172] and furthermore, as there is evidence that particular infectious agents - present at initiation of NIV - predict NIV failure [173], such aetiological differences might contribute to the linking of frequent exacerbations and mortality.

Clinical impact

It is of paramount importance to stress that inferences cannot be drawn from this study about the futility of either assisted ventilation or repeated ventilation. Firstly, the population studied was treated with assisted ventilation for the first time and is therefore neither generalisable to all COPD patients nor to COPD patients treated with repeated ventilation. Secondly, by design this study did not aim to make predictions, meeting this aim would have required another statistical set-up and validation in a

separate cohort. Thirdly, the difference between significant odds ratios and clinical impact should be appreciated.

1.3.3. STUDY II

A number of studies address the use of different modes of ventilation in COPD [63,86,87,174–182]. The surge in the use of NIV in our study mirrors the general international trend [86,175,178,179], although the use of NIV in Denmark commenced rather late. It is interesting that IMV has not lost foothold with the introduction of NIV, as NIV has been branded the most efficient treatment of choice for AECOPD and as declining use has been observed almost all other studies. The mortality rates found in the Danish population are in accordance with the rates seen in a recent European survey[183], but are somewhat higher than the rates found in the study by Chandra et al [86], which might be explained by case mix (e.g. higher admission rates, different discharge practice) in the US. Being a series of snapshots of clinical practice, study II does not allow firm conclusions regarding the shifts in treatment seen in our population but several hypotheses can be outlined to explain the increasing in-hospital mortality in the IMV-groups, which at a glance seems worrying. It must, however, be interpreted in the context of the changing practice. Figure 9 maps out some explanations for the increasing mortality over time in the IMV overall group.

Figure 9 Possible explanations for the increasing IMV in-hospital mortality over time.

Clinical impact

Surveys published at the time of our setting up study II[86,175] led us to assume that the use of IMV in Denmark would have declined in parallel with the increasing use of NIV. Any such decline however, was not observed. It might be that throughout the studied period of time IMV has been administered to those patients whose condition would at any time warrant the treatment. Alternatively, the introduction of NIV has freed ICU resources to be allocated to patients whose grim prognosis would formerly have led to their not being prioritised. If indeed more patients with high acute and chronic severity are offered a trial of IMV, future studies will have to clarify if this meaningfully prolongs life or extends the dying process.

1.3.4. STUDY III

A number of papers have examined anaemia in COPD [79,123,125–127,184–196]. In our study we did find a high prevalence of mainly mild anaemia, whereas grave anaemia and polycythaemia were rare. The prevalence spectrum reported in the literature is broad, ranging from less than 5% to more than 40%. The prevalence of 30.9 % in our populaltion is thus in accordance with previous studies. Apart from an American study that relied on diagnostic codes rather than actual haemoglobin measurements [127], ours is, to our knowledge, the largest study of anaemia prevalence in COPD so far and one of few concerned with anaemia in acute exacerbations. Importantly, our population is not selected based on absence of certain comorbidities, an exclusion which can explain the lower prevalence found in some papers [185]. Comorbidities might, paradoxically, also explain a higher prevalence found in a populations where diabetes [123] is common.

Selection of patients based on severity of acute illness might also shift the prevalence of anaemia. In a study where only patients receiving NIV were included [191], anaemia was more frequent than in our population but, in contrast, the prevalence was low among invasively ventilated patients [79]. The relation between severity of acute illness is very likely confounded by age and severity of stable phase COPD.

In our population, the lower the concentration of haemoglobin the higher the mortality after discharge. Though we are not aware of any large, directly comparable studies, a similar relation is seen among stable phase COPD patients [126].

Even mild anaemia was significantly associated with mortality in our study. In a sense, this mirrors a study of stage III/IV COPD patients, which also found that levels well above the lower normal range were associated with lower risk [194].

Clinical impact

The relationship between anaemia and mortality in our study strikingly resembles the pattern found in a large population of patients with heart failure [197], in as much as even mild anaemia associates with increased mortality, and mortality is lower the higher the haemoglobin concentration. One might even speculate that anemia is a general measure of morbidity in chronic disease? Should we completely rethink the concept of normal ranges in patients with chronic disease? The cautious but evasive answer to this is that we might have to be careful when we use normal ranges. We do not yet have evidence that targeted treatment of mild anaemia improves prognosis per se, but the results of study III imply that anaemic AECOPD patients constitute a high risk subpopulation who might benefit by close clinical surveillance and support.

PERSPECTIVES

At the end of the day, what is primarily important in the field of risk factor assessment is the identification of "red alerts" which should trigger some clinical action. Per se, observational studies will never answer questions of causality and will therefore not allow us to conclude that exacerbations should be prevented, that assisted ventilation should be used in a larger part of the population or that anaemia should be medically treated.

Though Hurst et al. did not find any correlation between haemoglobin and exacerbation frequency (possibly because haemoglobin was entered into the study as a linear predictor which might obliterate any correlation if the true association is U-shaped) [42], correlations have been found between haemoglobin and inflammatory markers respectively, and frequency of exacerbations [19,126,198]. It is an intriguing thought that the associations between previous exacerbations, haemoglobin, and numerous inflammatory markers respectively, and mortality might reflect aspects of the same pathological process whether this be systemic inflammation or another overarching "systemic component". In many studies, *relative* mortality significantly increased, but, to our knowledge, so far no predictor has explained a large *absolute* proportion of the variability in clinical courses. It might be that the impact of such a "systemic component" is limited, or, as mentioned, that hitherto applied proxies do not reflect the true exposure accurately. Another possible explanation is that all-cause mortality is too broad an outcome. To address the latter, an interesting future study would be to explore the associations between different types of anaemia or previous exacerbations and future events related to COPD progression (installation of domiciliary oxygen etc.).

The biological relevance of mapping the changing pattern of clinical actions and decisions lies primarily in the impact that such changes, if unrecognised, can have on conclusions drawn from studies of population incidence and risk factors. A thorough description of and adjustment for case mix is paramount to any epidemiological or clinical study and it is a fair critique of study II that that is exactly what we do *not* provide for our analysis of mortality over time, as we do not address changes in severity. Other studies have addressed the case mix, but most often the trade-off is a necessity to restrict data collection to critical care units[199], thereby the dissemination of treatments to wards is missed. What our study does uniquely provide is an estimate of the usage of assisted ventilation for AECOPD irrespective of where the treatment is administered and a suggestion that the price paid for multiplying the use of ventilation has not been an increased mortality. When results of not only venous but

also arterial blood tests become accessible, it will be possible to trace changes in case mix and its impact on mortality.

The organisational relevance of our study lies in our showing that, although NIV has gained a strong foothold in the treatment of AECOPD, there is, as the number of treatments has not declined, still a perception of benefit derived from IMV among Danish clinicians. We do not, however, know if this perception differs markedly among clinicians or among hospitals or if the treatment administered to a given COPD patient has changed or depends on factors not directly related to the clinical condition. In collaboration with British researchers I have set up a study of the between hospitals variation in the use of IMV. Setting the study in Great Britain allows us to adjust for case-mix and we aim to uncover if the propensity of some hospitals to use IMV markedly diverges from the national average.

Our observations indicate that haemoglobin levels below the reference range are grim prognostic markers, but we cannot ascertain whether low haemoglobin in itself negatively influences the clinical course, it merely correlates with a detrimental development as an innocent bystander or indeed is a beneficial compensatory mechanism without which the organism would be even worse off, though the latter is biologically unlikely. While intervention studies are ultimately required, observational studies gain their merit by generating hypotheses, by alerting researchers to potential harms, and by describing the make-up of the population that an intenvention should be targeted at. Our results are therefore relevant should a randomised trial of the impact of some intervention in AECOPD patients with anaemia be set up. Estimates of prevalence are relevant in power calculations, as is the strength of correlation between levels of haemoglobin and mortality for identification of a target population. Further prerequisites for deciding on a rational intervention in a trial would, however, be a thorough description of the frequency of different types of anaemia and how they respectively correlate with mortality. Our data did, as stated, unfortunately not allow us to explore this issue but a future study could be set up potentially involving a biobank to ensure that the collection of haematological parameters was not biased by sampling-by-indication.

CONCLUSION

In conclusion, the studies presented in this thesis support that both the previous history of exacerbations and the haemoglobin at admission are risk factors for mortality among AECOPD patients. Also, the introduction of non-invasive ventilation has evoked a profound change in the treatment of severe AECOPD, where more patients are treated with assisted ventilation without large changes in mortality among ventilated patients.

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Appendix

Literature searches

Study 1

The search strategy was to identify studies where the association between previous exacerbations and mortality following exacerbations were examined.

Pubmed was, as per June 14, 2016, searched for:

((((((((((((((((((((("previous admission") OR "previous admissions") OR "previous hospital admission") OR "previous hospital admissions") OR "frequency of exacerbation") OR "frequent exacerbation") OR "frequent exacerbations") OR "frequent aecopd")) OR subsequent severe exacerbation*[tiab]) OR subsequent exacerbation*[tiab]) OR second exacerbation*[tiab]) OR second severe exacerbation*[tiab])) OR frequency of severe exacerbation*[tiab]) OR exacerbation frequency[tiab])) OR exacerbation incidence*[tiab])) AND ((((((("Pulmonary Disease, Chronic Obstructive"[Mesh]) OR ((("chronic obstructive lung"[Title/Abstract]) OR "Chronic Obstructive Pulmonary"[Title/Abstract]) OR copd[Title/Abstract])))))) AND ((Danish[lang] OR English[lang] OR Norwegian[lang] OR Swedish[lang]))))) AND ("Mortality" OR "Death" OR "fatality" OR "fatal")))

This search yielded 198 papers.

An additional search in Embase at the time the study was conducted had retrieved 489 papers.

A primary sorting by title and abstract was conducted and doublets were removed.

A secondary sorting was conducted based on the entire text. Reference lists in key papers were searched and 21 relevant papers were retrieved in total.

Study II

Pubmed was, as per June 16, 2016, searched for:

((((trend[tw] OR trends[tw])) OR "trends"[Subheading])) AND (((((((assisted ventilation*[tw]) OR Mechanical Ventilation*[tw]) OR "Respiration, Artificial"[Mesh]) OR Non invasive Ventilation*[tw]) OR Noninvasive Ventilation*[tw])) AND ((((((("Pulmonary Disease, Chronic Obstructive"[Mesh]) OR "chronic obstructive lung"[tw]) OR "Chronic Obstructive Pulmonary"[tw]) OR copd[tw]) OR Chronic Obstructive Airway[tw]) OR Chronic Airflow Obstruction*[tw]))

The search yielded 148 hits

An additional search in Embase at the time the study was planned yielded 157 papers.

A primary sorting by title and abstract was conducted and doublets were removed.

A secondary sorting was conducted based on the entire text. Papers concerned with the use of ventilation for patients with acute COPD - or from which information regarding subgroups with COPD could be extracted - were considered.

Referencelists in key papers were searched and 12 relevant papers were retrieved in total.

Study III

A Pubmed/Embase search was undertaken to identify studies in which the association between concentrations of haemoglobin (which could also be expressed as haematocrit) and mortality was assessed.

Pubmed was, as per June 14, 2016, searched for:

((((((((((("Pulmonary Disease, Chronic Obstructive"[Mesh]) OR ((("chronic obstructive lung"[tw]) OR "Chronic Obstructive Pulmonary"[tw]) OR copd[tw])))))))) OR Chronic Obstructive Airway[tw]) OR Chronic Airflow Obstruction*[tw])) AND ((((((("Mortality"[Mesh]) OR Mortalit*[tw]) OR "mortality"[Subheading]) OR "Death"[Mesh]) OR Death*[tw]) OR Survival[tw])) AND ((((((((("Anemia"[Mesh]) OR Anemia*[tw]) OR "Hemoglobins"[Mesh]) OR Hemoglobin*[tw]) OR Haemoglobin*[tw]) OR Anaemia*[tw]) OR haematocrit[tw]) OR hematocrit[tw]) OR hgb[tw]) OR polycyt*[tw])

This search yielded 311 papers.

An additional search in Embase was conducted at the time of the study.

A primary sorting by title and abstract was conducted and doublets were removed.

A secondary sorting was based on the entire text, and identified studies concerned with anaemia and mortality and/or serious adverse events from which estimates of risk could be inferred. The reference lists of key papers were likewise searched and yielded 18 papers in total.

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